NATIONAL GUIDELINE CLEARINGHOUSE™ (NGC)
GUIDELINE SYNTHESIS

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)
PART I. DIAGNOSIS AND MANAGEMENT OF STABLE COPD

Guidelines

1. Update Finnish Medical Society Duodecim. Chronic obstructive pulmonary disease (COPD). In: EBM Guidelines. Evidence-Based Medicine [CD-ROM]. Helsinki, Finland: Duodecim Medical Publications Ltd.; 2005 Mar 2 [various]. [37 references]
2. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD):Global Initiative for Chronic Obstructive Lung Disease, 2005. 115 p.
3. National Collaborating Centre for Chronic Conditions, National Institute for Health and Clinical Excellence (NCCCC/NICE). Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. Thorax 2004 Feb;59 Suppl 1:1-232. [491 references]

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INTRODUCTION

A direct comparison of the Finnish Medical Society Duodecim (FMS), the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (a collaborative project of the World Health Organization and the National Heart, Lung, and Blood Institute), and the National Collaborating Centre for Chronic Conditions (a collaborating center for the National Institute for Health and Clinical Excellence [NCCCC/NICE]) recommendations for the diagnosis and management of chronic obstructive pulmonary disease (COPD) is provided in the tables below. All three guidelines are broad in scope, providing recommendations on diagnosis and management of both stable COPD and acute exacerbations of disease. Both the GOLD and NCCCC/NICE guidelines also address prevention strategies and pulmonary rehabilitation. NCCCC/NICE also provides recommendations for drug delivery systems (including inhalers, spacers, and nebulizers) and the management of pulmonary hypertension and cor pulmonale. Recommendations for the diagnosis and management of acute exacerbations of COPD are compared in Part II of this synthesis. Recommendations for pulmonary rehabilitation of patients with COPD are addressed in Part III of this synthesis (currently under development).

Table 1 provides the scope of the guidelines, Table 2 compares the major recommendations, and Table 3 compares the potential benefits and harms of implementing the recommendations. Definitions for the levels of evidence used to support the guideline recommendations are given in Table 4

Following the content and recommendation comparison tables, the areas of agreement and differences among the guidelines are identified. The evidence surrounding disparate recommendations is explored in the discussion of areas of difference.

Related Guidelines

- Institute for Clinical Systems Improvement (ICSI). Chronic obstructive pulmonary disease. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2005 Dec. 66 p. [122 references]
- American Medical Directors Association (AMDA). COPD management in the long-term care setting. Columbia (MD): American Medical Directors Association (AMDA); 2003. 32 p. [15 references]
- American Academy of Family Physicians (AAFP), American Dietetic Association (ADA), Nutrition Screening Initiative (NSI). Chronic obstructive pulmonary disease. Nutrition management for older adults. Washington (DC): Nutrition Screening Initiative (NSI); 2002. 11 p. [38 references]
- Department of Defense (DoD), Department of Veterans Affairs (DVA), Veterans Health Administration (VHA) The pharmacologic management of chronic obstructive pulmonary disease. Washington (DC): Veterans Health

Administration, Department of Veterans Affairs; 2002 Sep. 31 p. [157 references]
- Intracorp Chronic obstructive pulmonary disease. Philadelphia (PA): Intracorp; 2004. Various p.

Abbreviations used in the text and table:

- AAT, Alpha1-antitrypsin
- BMI, Body mass index
- COPD, Chronic obstructive pulmonary disease
- ERS, European Respiratory Society
- FMS, Finnish Medical Society Duodecim
- FEV_1, Forced expiratory volume in one second
- FVC, Forced vital capacity
- GOLD, Global Initiative for Chronic Obstructive Lung Disease
- LTOT, Long-term oxygen therapy
- LVRS, Lung volume reduction surgery
- MRC, Medical Research Council
- NCCCC, National Collaborating Centre for Chronic Conditions
- NICE, National Institute for Health and Clinical Excellence
- PEF, Peak expiratory flow
- PEP, Positive expiratory pressure
- SAIBA, Short-acting inhaled $beta_2$ agonist
- T_LCO, Transfer factor for carbon monoxide
- VHA/DOD, Veterans Health Administration/Department of Veterans Affairs
- VC, Vital capacity

TABLE 1: COMPARISON OF SCOPE AND CONTENT	
Objective and Scope	
FMS (2005)	• Evidence-Based Medicine Guidelines collect, summarize, and update the core clinical knowledge essential in general practice. The guidelines also describe the scientific evidence underlying the given recommendations.
GOLD (2005)	• To recommend effective COPD management and prevention strategies for use in all countries • To increase awareness of the medical community, public health officials, and the general public that COPD is a public health problem • To decrease morbidity and mortality from COPD through implementation and evaluation of effective programs for diagnosis and management • To improve prevention and management of COPD through implementation and evaluation of effective programs for diagnosis and management

	• To encourage renewed research interest in this highly prevalent disease
NCCCC/NICE (2004)	• To develop a clinical guideline on the management of chronic obstructive pulmonary disease for use in the National Health Service (NHS) in England and Wales • To offer best practice advice on the identification and care of patients with COPD • To define the symptoms, signs, and investigations required to establish a diagnosis of COPD • To define the factors that are necessary to assess the severity of COPD, provide prognostic information, and guide best management • To provide guidance on the pharmacological and non-pharmacological treatment of patients with stable COPD and on the management of exacerbations • To discuss the interface with surgery and intensive therapy units
Target Population	
FMS (2005)	• Finland • Adults with COPD • Adults requiring evaluation for possible chronic obstructive pulmonary disease Note: This guideline includes recommendations for patients with both chronic stable disease and patients with acute exacerbations of COPD. Recommendations concerning acute exacerbations are provided in Part II of this synthesis
GOLD (2005)	• Individuals with COPD Note: This guideline includes recommendations for patients with both chronic stable disease and patients with acute exacerbations of COPD. Recommendations concerning acute exacerbations are provided in Part II of this synthesis
NCCCC/NICE (2004)	• England and Wales • Adults who have a clinical working diagnosis of COPD, including chronic bronchitis, emphysema, and chronic airflow limitation/obstruction Note: The guideline does not cover the management of people with asthma, bronchopulmonary dysplasia, and bronchiectasis, nor does it cover children. Note: This guideline includes recommendations for patients with both chronic stable disease and patients with acute exacerbations of COPD. Recommendations concerning acute exacerbations are provided in Part II of this synthesis
Intended Users	

FMS (2005)	Health Care Providers Physicians
GOLD (2005)	Advanced Practice Nurses Allied Health Personnel Nurses Physician Assistants Physicians Public Health Departments Respiratory Care Practitioners
NCCCC/NICE (2004)	Advanced Practice Nurses Allied Health Personnel Dietitians Health Care Providers Hospitals Nurses Occupational Therapists Patients Physical Therapists Physicians Public Health Departments Respiratory Care Practitioners Students
Interventions and Practices Considered	
FMS (2005)	Diagnosis/Assessment 1. Identification of signs and symptoms and/or key indicators for COPD 2. Differential diagnosis 3. Physical examination 4. Spirometry 5. Bronchodilator reversibility testing 6. Measurement of arterial blood gases/oximetry 7. Chest x-ray 8. Further investigations, as needed, including full blood count, body mass index, computed tomography scan 9. Assessment of severity of COPD 10. Referral for specialist advice Management/Treatment 1. Smoking cessation (including pharmacological and non-pharmacological approaches) 2. Pharmacologic therapy, including: • Bronchodilators (short-acting and long-acting $beta_2$-agonist and/or anticholinergics, both inhaled and oral formulations)

	• Theophylline • Inhaled and oral corticosteroid therapy • Combination therapy 3. Other pharmacologic therapies such as: • Vaccination (pneumococcal, influenza) • Antibiotics • Mucolytics 4. Non-pharmacological interventions including pulmonary rehabilitation, lifestyle advice, and education in self-management techniques 5. Oxygen therapy 6. Surgery, including bullectomy, lung volume reduction, transplant Note: For specific interventions concerning diagnosis and management of acute exacerbations of COPD, see Part II of this synthesis.
GOLD (2005)	Diagnosis/Assessment 1. Identification of signs and symptoms and/or key indicators for COPD 2. Differential diagnosis 3. Medical history 4. Physical examination 5. Spirometry 6. Bronchodilator reversibility testing 7. Measurement of arterial blood gases/oximetry 8. Chest x-ray 9. Measurement of AAT levels 10. Further investigations, as needed, including full blood count, body mass index, computed tomography scan 11. Assessment of severity of COPD 12. Referral for specialist advice Management/Treatment 1. Smoking cessation (including pharmacological and non-pharmacological approaches) 2. Pharmacologic therapy, including: • Bronchodilators (short-acting and long-acting $beta_2$-agonist and/or anticholinergics, both inhaled and oral formulations) • Theophylline • Inhaled and oral corticosteroid therapy • Combination therapy 3. Other pharmacologic therapies such as: • Vaccination (pneumococcal, influenza) • AAT replacement therapy in the management of patients with AAT deficiency • Antibiotics • Antitussives

	• Mucolytics 4. Non-pharmacological interventions including pulmonary rehabilitation, lifestyle advice, and education in self-management techniques 5. Oxygen therapy 6. Surgery, including bullectomy, lung volume reduction, transplant 7. Follow up Note: For specific interventions concerning diagnosis and management of acute exacerbations of COPD, see Part II of this synthesis. For interventions on pulmonary rehabilitation, see Part III of this synthesis (under development)
NCCCC/NICE (2004)	Diagnosis/Assessment 1. Identification of signs and symptoms of COPD 2. Spirometry 3. Differential diagnosis 4. Further investigations including chest x-ray, full blood count, body mass index 5. Additional investigations as needed including serial domiciliary peak flow measurement, measurement of AAT levels, transfer factor for carbon monoxide, computed tomography scan of the thorax, electrocardiogram, echocardiogram, pulse oximetry, sputum culture 6. Reversibility testing (considered but not routinely recommended) 7. Assessment of severity of COPD 8. Identification of early disease 9. Referral for specialist advice Management/Treatment of Stable COPD 1. Smoking cessation 2. Pharmacologic therapy, including: • Inhaled bronchodilators (short-acting and long-acting beta$_2$-agonist and/or anticholinergics, both inhaled and oral formulations) • Theophylline • Inhaled and oral corticosteroid therapy • Combination therapy 3. Other pharmacologic therapies such as: • Vaccination and anti-viral therapy (pneumococcal, influenza) • AAT replacement therapy in the management of patients with AAT deficiency • Prophylactic antibiotics • Antitussives • Mucolytics 4. Non-pharmacological interventions including pulmonary rehabilitation, lifestyle advice, and education in self-

	management techniques 5. Oxygen therapy 6. Lung surgery, including bullectomy, lung volume reduction, transplant 7. Follow up Note: For specific interventions concerning diagnosis and management of acute exacerbations of COPD, see Part II of this synthesis. For interventions on pulmonary rehabilitation, see Part III of this synthesis (under development).

TABLE 2: COMPARISON OF RECOMMENDATIONS FOR THE DIAGNOSIS AND MANAGEMENT OF STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)	
DIAGNOSIS AND INITIAL ASSESSMENT	
Definition of COPD	
FMS (2005)	COPD: the patient has chronic, progressive airway obstruction, with no significant response to treatment. Other typical findings include chronic bronchitis and emphysema in varying grades depending on the patient. • Chronic bronchitis: sputum at least for 3 months in 2 consecutive years • Pulmonary emphysema: terminal air spaces widen and alveolar walls rupture
GOLD (2005)	COPD is a disease characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. A diagnosis of COPD should be considered in any patient who has symptoms of cough, sputum production, or dyspnea, and/or a history of exposure to risk factors for the disease.
NCCCC/NICE (2004)	COPD is characterized by airflow obstruction. The airflow obstruction is usually progressive, not fully reversible and does not change markedly over several months. The disease is predominantly caused by smoking. • Airflow obstruction is defined as a reduced FEV_1 and a reduced FEV_1/FVC ratio, such that FEV_1 is less than 80% predicted and FEV_1/FVC is less than 0.7. • The airflow obstruction is due to a combination of airway and parenchymal damage.

	• The damage is the result of chronic inflammation that differs from that seen in asthma and which is usually the result of tobacco smoke. • Significant airflow obstruction may be present before the individual is aware of it. • COPD produces symptoms, disability, and impaired quality of life which may respond to pharmacological and other therapies that have limited or no impact on the airflow obstruction. • COPD is now the preferred term for the conditions in patients with airflow obstruction who were previously diagnosed as having chronic bronchitis or emphysema. • Other factors, particularly occupational exposures, may also contribute to the development of COPD. There is no single diagnostic test for COPD. Making a diagnosis relies on clinical judgement based on a combination of history, physical examination and confirmation of the presence of airflow obstruction using spirometry.
Symptoms/Medical History	
FMS (2005)	Symptoms • Cough and sputum excretion are common symptoms of chronic bronchitis. • Patients with progressive disease suffer from slowly increasing dyspnoea during exercise. • The symptoms are aggravated by respiratory infection.

GOLD (2005)	A diagnosis of COPD should be considered in any patient who has cough, sputum production, or dyspnea, and/or a history of exposure to risk factors for the disease. The diagnosis is confirmed by an objective measure of airflow limitation, preferably spirometry.
	
	Key Indicators for Considering a Diagnosis of COPD
	
	• Chronic cough: Present intermittently or every day. Often present throughout the day; seldom only nocturnal
	• Chronic sputum production: Any pattern of chronic sputum production may indicate COPD
	• Dyspnea that is:
	  • Progressive (worsens over time)
	  • Persistent (present every day)
	  • Described by the patient as: "increased effort to breathe," "heaviness," "air hunger," or "gasping"
	  • Worse on exercise
	  • Worse during respiratory infections

	• History of exposure to risk factors, especially:
	  • Tobacco smoke
	  • Occupational dusts and chemicals
	  • Smoke from home cooking and heating fuels
	
	Medical History: A detailed medical history of a new patient known or thought to have COPD should assess:
	
	• Exposure to risk factors
	• Past medical history, including asthma, allergy, sinusitis or nasal polyps, respiratory infections in childhood, and other respiratory diseases
	• Family history of COPD or other chronic respiratory disease
	• Pattern of symptom development
	• History of exacerbations or previous hospitalizations for respiratory disorder
	• Presence of comorbidities, such as heart disease and rheumatic disease, that may also contribute to restriction of activity
	• Appropriateness of current medical treatments
	• Impact of disease on patient's life, including limitation of activity; missed work and economic impact; effect on family routines; and feelings of depression or anxiety
	• Social and family support available to the patient
	• Possibilities for reducing risk factors, especially smoking cessation

NCCCC/NICE (2004)	The diagnosis of COPD depends on thinking of it as a cause of breathlessness or cough. The diagnosis is suspected on the basis of symptoms and signs and supported by spirometry. Symptoms D - A diagnosis of COPD should be considered in patients over the age of 35 who have a risk factor (generally smoking) and who present with one or more of the following symptoms: • Exertional breathlessness • Chronic cough • Regular sputum production • Frequent winter "bronchitis" • Wheeze D - Patients in whom a diagnosis of COPD is considered should also be asked about the presence of the following factors: • Weight loss • Effort intolerance • Waking at night

	• Ankle swelling • Fatigue • Occupational hazards • Chest pain • Haemoptysis Note: These last two symptoms are uncommon in COPD and raise the possibility of an alternative diagnosis. D - One of the primary symptoms of COPD is breathlessness. The Medical Research Council (MRC) dyspnoea scale (for an adaptation of the scale, see Table 3 in the original guideline document) should be used to grade the breathlessness according to the level of exertion required to elicit it.
Physical Examination	

FMS (2005)	• Most patients seek a doctor late, when the disease is already moderate to severe. In mild disease auscultation may be normal and no auscultatory signs for obstruction can be detected.
	• The following symptoms indicate severe COPD; their absence does not exclude the existense of mild COPD:
	  • Because of airway obstruction, wheezing rattles may be heard at the end of forced expiration.
	  • The patient with advanced emphysema may have a barrel-chested appearance, on auscultation silent respiratory sounds are heard, and on percussion the sound is hypersonor.
	  • Cyanosis is associated with hypoxaemia.

GOLD (2005)	Though an important part of patient care, a physical examination is rarely diagnostic in COPD. Physical signs of airflow limitation are rarely present until significant impairment of lung function has occurred, and their detection has a relatively low sensitivity and specificity. Inspection • Central cyanosis, or bluish discoloration of the mucosal membranes, may be present but is difficult to detect in artificial light and in many racial groups. • Common chest wall abnormalities, which reflect the pulmonary hyperinflation seen in COPD, include relatively horizontal ribs, "barrel-shaped" chest, and protruding abdomen. • Flattening of the hemi-diaphragms may be associated with paradoxical in-drawing of the lower rib cage on inspiration, reduced cardiac dullness, and widening xiphisternal angle.

	• Resting respiratory rate is often increased to more than 20 breaths per minute and breathing can be relatively shallow. • Patients commonly show pursed-lip breathing, which may serve to slow expiratory flow and permit more efficient lung emptying. • COPD patients often have resting muscle activation while lying supine. Use of the scalene and sternocleidomastoid muscles is a further indicator of respiratory distress. • Ankle or lower leg edema can be a sign of right heart failure. Palpation and Percussion • These are often unhelpful in COPD. • Detection of the heart apex beat may be difficult due to pulmonary hyperinflation. • Hyperinflation also leads to downward displacement of the liver and an increase in the ability to palpate this organ without it being enlarged. Auscultation • Patients with COPD often have reduced breath sounds, but this finding is not sufficiently characteristic to make the diagnosis. • The presence of wheezing during quiet breathing is a useful pointer to airflow limitation. However, wheezing heard only after forced expiration is of no diagnostic value. • Inspiratory crackles occur in some COPD patients but are of little help diagnostically. • Heart sounds are best heard over the xiphoid area.
NCCCC/NICE (2004)	No recommendations offered.
Measurement of Airflow Limitation--Spirometry	
FMS (2005)	Early diagnosis by spirometry combined with active promotion of smoking cessation is pursued. According to the international criteria, the threshold value for the diagnosis of mild COPD is FEV_1/FVC <70% after the bronchodilating test, when FEV% is >80%.
GOLD (2005)	To help identify patients earlier in the course of the disease, spirometry should be performed for patients who have chronic cough and sputum production and a history of exposure to risk factors, even if they do not have dyspnea. Spirometry should measure the maximal volume of air forcibly exhaled from the point of maximal inhalation (FVC) and the volume of air exhaled

	during the first second of this maneuver (FEV_1), and the ratio of these two measurements (FEV_1/FVC) should be calculated. Patients with COPD typically show a decrease in both FEV_1 and FVC. The presence of a postbronchodilator FEV_1 <80% of the predicted value in combination with an FEV_1/FVC <70% confirms the presence of airflow limitation that is not fully reversible. The FEV_1/FVC on its own is a more sensitive measure of airflow limitation, and an FEV_1/FVC <70% is considered an early sign of airflow limitation in patients whose FEV_1 remains normal ($\geq$80% predicted). This approach to defining airflow limitation is a pragmatic one in view of the fact that universally applicable reference values for FEV_1 and FVC are not available.
NCCCC/NICE (2004)	D - Spirometry should be performed: • At the time of diagnosis • To reconsider the diagnosis if patients show an exceptionally good response to treatment D - All health professionals managing patients with COPD should have access to spirometry and be competent in the interpretation of the results. D - Spirometry can be performed by any healthcare worker who has undergone appropriate training and who keeps his or her skills up to date. D - Spirometry services should be supported by quality control processes. D - It is recommended that European Respiratory Society (ERS) 1993 reference values* are used but it is recognised that these values may lead to under-diagnosis in the elderly and are not applicable in black and Asian populations. *Quanjer PH, Tammeling GJ, Cotes JE et al. (1993) Lung volumes and forced ventilator flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J (Suppl) 16:5-40. Identification of Early Disease D - Spirometry should be performed in patients who are over 35, current or ex-smokers, and have a chronic cough. B - Spirometry should be considered in patients with chronic bronchitis. A significant proportion of these will go on to develop airflow limitation.
Differential Diagnosis	

FMS (2005)	Most important differential diagnostic problem is asthma. Also many asthmatics smoke.
GOLD (2005)	A major differential diagnosis is asthma. In some patients with chronic asthma, a clear distinction from COPD is not possible using current imaging and physiological testing techniques. In these cases, current management is similar to that of asthma. Other potential diagnoses are usually easier to distinguish from COPD. Suggestive features for respective diseases are presented below: COPD • Onset in mid-life • Symptoms slowly progressive • Long smoking history • Dyspnea during exercise • Largely irreversible airflow limitation Asthma • Onset early in life (often childhood) • Symptoms vary from day to day • Symptoms at night/early morning • Allergy, rhinitis, and/or eczema also present • Family history of asthma • Largely reversible airflow limitation Congestive Heart Failure • Fine basilar crackles on auscultation • Chest x-ray shows dilated heart, pulmonary edema. • Pulmonary function tests indicate volume restriction, not airflow limitation Bronchiectasis • Large volumes of purulent sputum • Commonly associated with bacterial infection • Coarse crackles/clubbing on auscultation • Chest x-ray/computed tomography shows bronchial dilation, bronchial wall thickening. Tuberculosis • Onset all ages • Chest x-ray shows lung infiltrate or nodular lesions. • Microbiological confirmation

	• High local prevalence of tuberculosis Obliterative Bronchiolitis • Onset in younger age, nonsmokers • May have history of rheumatoid arthritis or fume exposure • Computed tomography on expiration shows hypodense areas. Diffuse Panbronchiolitis • Most patients are male and nonsmokers. • Almost all have chronic sinusitis chest x-ray and high resolution computed tomography (HRCT) show diffuse small centrilobular nodular opacities and hyperinflation. Note: These features tend to be characteristic of the respective diseases, but do not occur in every case. For example, a person who has never smoked may develop COPD (especially in the developing world, where other risk factors may be more important than cigarette smoking); asthma may develop in adult and even elderly patients.

NCCCC/NICE (2004)	D - COPD and asthma are frequently distinguishable on the basis of history (and examination) in untreated patients presenting for the first time. Features from the history and examination should be used to differentiate COPD from asthma whenever possible.
	
	Clinical features differentiating COPD and asthma include:
	
	• Smoker or ex-smoker:
	  • COPD: nearly all
	  • Asthma: possibly
	• Symptoms under age 35:
	  • COPD: rare
	  • Asthma: common
	  • Chronic productive cough:
	  • COPD: common
	  • Asthma: uncommon
	• Breathlessness:
	  • COPD: persistent and progressive
	  • Asthma: variable
	• Night time waking with breathlessness and/or wheeze:
	  • COPD: uncommon
	  • Asthma: common
	• Significant diurnal or day to day variability of symptoms:
	  • COPD: uncommon
	  • Asthma: common
	
	D - Longitudinal observation of patients (whether using spirometry, peak flow, or symptoms) should also be used to help differentiate COPD from asthma.

Bronchodilator Reversibility Testing	
FMS (2005)	Test with a bronchodilating drug • The response to a bronchodilating drug is measured either by spirometry that is combined with a dose of a broncholytic drug (e.g., inhaled salbutamol 400 micrograms) or by PEF-measurements performed before and after the administration of the drug. In COPD, there is no response (cf. asthma).
GOLD (2005)	Generally performed only once, at the time of diagnosis of moderate COPD and beyond, this test is useful for several reasons: • To help rule out a diagnosis of asthma • To establish a patient's best attainable lung function at that point in time • To gauge a patient's prognosis • To assess potential response to treatment <u>Bronchodilator Reversibility Testing</u> Preparation • Tests should be performed when patients are clinically stable and free from respiratory infection. • Patients should not have taken inhaled short-acting bronchodilators in the previous six hours, long-acting beta$_2$-agonists in the previous 12 hours, or sustained-release theophyllines in the previous 24 hours. Spirometry • FEV_1 should be measured before a bronchodilator is given. • The bronchodilator should be given by metered dose inhaler through a spacer device or by nebulizer to be certain it has been inhaled. • The bronchodilator dose should be selected to be high on the dose/response curve. • Suitable dosage protocols are 400 micrograms beta$_2$-agonist, 80 micrograms anticholinergic, or the two combined. FEV_1 should be measured again 30 to 45 minutes after the bronchodilator is given. Results • An increase in FEV_1 that is both greater than 200 mL and 12% above the pre-bronchodilator FEV_1 is considered

	significant.
NCCCC/NICE (2004)	D - In most patients, routine spirometric reversibility testing is not necessary as a part of the diagnostic process or to plan initial therapy with bronchodilators or corticosteroids. It may be unhelpful or misleading because: • B - Repeated FEV_1 measurements can show small spontaneous fluctuations. • B - The results of a reversibility test performed on different occasions can be inconsistent and not reproducible. • B - Over-reliance on a single reversibility test may be misleading unless the change in FEV_1 is greater than 400 mL. • B - The definition of the magnitude of a significant change is purely arbitrary. • A - Response to long-term therapy is not predicted by acute reversibility testing. D - To help resolve cases where diagnostic doubt remains, or both COPD and asthma are present, the following findings should be used to help identify asthma: • A large (greater than 400 mL) response to bronchodilators • A large (greater than 400 mL) response to 30 mg oral prednisolone daily for 2 weeks • Serial peak flow measurements showing 20% or greater diurnal or day-to-day variability Clinically significant COPD is not present if the FEV_1 and FEV_1/ FVC ratio return to normal with drug therapy. D - If patients report a marked improvement in symptoms in response to inhaled therapy, the diagnosis of COPD should be reconsidered.
Chest X-ray	
FMS (2005)	Chest x-ray is of limited value in COPD diagnosis.
GOLD (2005)	A chest x-ray is seldom diagnostic in COPD unless obvious bullous disease is present, but it is valuable in excluding alternative diagnoses.
NCCCC/NICE (2004)	D - At the time of their initial diagnostic evaluation, in addition to spirometry all patients should have a chest radiograph to exclude other pathologies

Measurement of Arterial Blood Gases/Oximetry	
FMS (2005)	Blood gas analysis • In late stages of COPD arterial blood oxygen partial pressure (pO_2) decreases and carbon dioxide partial pressure (pCO_2) may increase.
GOLD (2005)	In advanced COPD, measurement of arterial blood gases is important. This test should be performed in patients with FEV_1 <40% predicted or with clinical signs suggestive of respiratory failure or right heart failure. Clinical signs of respiratory failure include central cyanosis, ankle swelling, and an increase in the jugular venous pressure. Clinical signs of hypercapnia are extremely nonspecific outside of acute exacerbations. Respiratory failure is indicated by a PaO_2 <8.0 kPa (60 mm Hg) with or without $PaCO_2$ >6.7 kPa (50 [millimeters] mm Hg) while breathing air at sea level. Measurement of arterial blood gases should be obtained by arterial puncture; finger or ear oximeters for assessing arterial oxygen saturation (SaO_2) are less reliable.
NCCCC/NICE (2004)	D - Additional investigations should be performed to aid management in some circumstances, including: • Pulse oximetry - To assess need for oxygen therapy; if cyanosis or cor pulmonale present, or if FEV_1
Measurement of Alpha-1 Antitrypsin (AAT) Levels	
FMS (2005)	Deficiency of alpha-1 antitrypsin is noted as a rare cause of emphysema in young patients.
GOLD (2005)	In patients who develop COPD at a young age (<45 years) or who have a strong family history of the disease, it may be valuable to identify coexisting AAT deficiency. This could lead to family screening or appropriate counseling. A serum concentration of ATT below 15 to 20% of the normal value is highly suggestive of homozygous AAT deficiency.
NCCCC/NICE (2004)	D - Additional investigations should be performed to aid management in some circumstances, including: • Alpha-1 antitrypsin - if early onset, minimal smoking history or family history D - Patients identified as having alpha-1 antitrypsin deficiency should be offered the opportunity to be referred to a specialist

	centre to discuss the clinical management of this condition.
Additional Investigations	

FMS (2005)	• The effectiveness of anti-inflammatory treatment is evaluated with a trial of steroids.
	  • Oral prednisolone, initially 30 to 40 mg/day (if necessary, give protection against ulcers, e.g., a proton pump inhibitor), or inhaled steroid (e.g., budesonide 400 to 800 micrograms twice daily). In oral administration the duration of the trial is 2 weeks, with an inhaled steroid 6 weeks.
	  • An objective response (PEF increase >20% and/or FEV1 increase >12% and at least 200 mL) is indicative of asthma.
	• Diffusion capacity
	  • Decreased in COPD

GOLD (2005)	Computed tomography (CT) of the chest is not routinely recommended. However, when there is doubt about the diagnosis of COPD, high resolution computed tomography (HRCT) might help in the differential diagnosis. In addition, if a surgical procedure such as bullectomy or lung volume reduction is contemplated, chest computed tomography is helpful.
NCCCC/NICE (2004)	D - At the time of their initial diagnostic evaluation, in addition to spirometry and chest radiograph all patients should have: • A full blood count to identify anaemia or polycythaemia • BMI calculated D - Additional investigations should be performed to aid management in some circumstances (see Additional Investigations below). Additional Investigations: • Serial domiciliary peak flow instruments - To exclude asthma if diagnostic doubt remains • Transfer factor for carbon monoxide (T_LCO) - To investigate symptoms that seem disproportionate to the spirometric impairment • Computed tomography (CT) scan of the thorax - To investigate symptoms that seem disproportionate to the spirometric impairment; to investigate abnormalities seen on a chest radiograph; to assess suitability for surgery • Electrocardiogram (ECG) - To assess cardiac status if features of cor pulmonale • Echocardiogram - To assess cardiac status if features of

	cor pulmonale • Sputum culture - To identify organisms if sputum is persistently present and purulent
Assessing Severity of Disease	
FMS (2005)	Mild disease: • Asymptomatic patients • Patients with occasional symptoms (generally FEV_1 >50% predicted) Continuous symptoms (FEV_1 generally <50% predicted)
GOLD (2005)	Assessment of COPD severity is based on the patient's level of symptoms, the severity of the spirometric abnormality, and the presence of complications such as respiratory failure and right heart failure. For educational reasons, a simple classification of disease severity into 5 stages is recommended. The staging is based on airflow limitation as measured by spirometry, which is essential for diagnosis and provides a useful description of the severity of pathological changes in COPD. Specific FEV_1 cut-points (e.g., <80% predicted) are used for the purposes of simplicity: these cut-points have not been clinically validated. Stage 0 [At Risk]: • Normal spirometry • Chronic symptoms (cough, sputum, production) Stage I [Mild COPD]: • FEV_1/FVC <70% • FEV_1 $\geq$80% predicted • With or without chronic symptoms (cough, sputum production) Stage II [Moderate COPD]: • FEV_1/FVC <70% • 50% $\leq FEV_1$ <80% predicted • With or without chronic symptoms (cough, sputum production) Stage III [Severe COPD]:

	• FEV_1/FVC <70% • 30% ≤FEV_1 <50% predicted Stage IV [Very Severe COPD]: • FEV_1/FVC <70% • FEV_1 <30% predicted or FEV_1 <50% predicted plus chronic respiratory failure
NCCCC/NICE (2004)	COPD is heterogeneous, so no single measure can give an adequate assessment of the true severity of the disease in an individual patient. Severity assessment is, nevertheless, important because it has implications for therapy and relates to prognosis. D - Mild airflow obstruction can be associated with significant disability in patients with COPD. A true assessment of severity should include assessment of the degree of airflow obstruction and disability, the frequency of exacerbations and the following known prognostic factors: • FEV_1 • T_LCO • Breathlessness (MRC scale) • Health status • Exercise capacity • BMI • Partial pressure of oxygen in arterial blood (PaO_2) • Cor pulmonale. D - The severity of airflow obstruction should be assessed according to the reduction in FEV_1 as follows: • Mild airflow obstruction: 50 to 80% predicted FEV_1 • Moderate airflow obstruction: 30 to 49% predicted FEV_1 • Severe airflow obstruction: <30% predicted FEV_1
MANAGEMENT OF STABLE COPD	
Overall Management Strategy	
FMS (2005)	No overall management strategy is provided. Basic rules for drug therapy, according to disease severity are provided (see below).
GOLD (2005)	The overall approach to managing stable COPD should be characterized by a stepwise increase in treatment, depending on the severity of the disease. The management strategy is based

	on an individualized assessment of disease severity and response to various therapies. Disease severity is determined by the severity of symptoms and airflow limitation, as well as other factors such as the frequency and severity of exacerbations, complications, respiratory failure, comorbidities (cardiovascular disease, sleep related disorders, etc.), and the general health status of the patient. Treatment also depends on the patient's educational level and willingness to apply the recommended management, on cultural and local conditions, and on the availability of medications.
NCCCC/NICE (2004)	The management of an individual patient's disease should be guided by the symptoms and disability that they experience. At different times in the natural history of their disease different features may predominate and their management will change to reflect this.
General Approach to Pharmacologic Therapy	

FMS (2005)	Basic Rules of Drug Therapy
	
	Mild disease
	
	• Asymptomatic patients
	  • No drug therapy
	• Patients with occasional symptoms (generally FEV1>50% predicted)
	  • Anticholinergics or short-acting beta-2-agonists according to clinical response
	  • Trial of steroids if asthma is suspected
	
	Continuous symptoms (FEV_1 generally
	
	• Anticholinergics and short-acting beta-2-agonists (combined) according to clinical response or
	• Long acting anticholinergic or beta-2-agonist, or their combination
	• In selected cases inhaled glucocorticoid if frequent exacerbations
	• Trial of theophylline if symptoms persist [A]
	• Surgery (bullectomy, lung transplantation, lung volume reduction) can be recommended only to a small subset of the patients after careful evaluation.

GOLD (2005)	Pharmacologic therapy is used to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status, and improve exercise tolerance. None of the existing medications for COPD has been shown to modify the long-term decline in lung function that is the hallmark of this

	disease. However, this should not preclude efforts to use medications to control symptoms.
NCCCC/NICE (2004)	Key Priorities for Implementation • Long-acting inhaled bronchodilators (beta$_2$-agonists and/or anticholinergics) should be used to control symptoms and improve exercise capacity in patients who continue to experience problems despite the use of short-acting drugs. • Inhaled corticosteroids should be added to long-acting bronchodilators to decrease exacerbation frequency in patients with an FEV_1 less than or equal to 50% predicted who have had two or more exacerbations requiring treatment with antibiotics or oral corticosteroids in a 12-month period.
Bronchodilators	

FMS (2005)	• Inhaled short acting (ipratropium [B] or oxitropium bromide) or long acting (tiotropium [A]) anticholinergic drug
	  • First line treatment
	  • The dose must be high enough; administration 4 to 6 times daily with the short acting drug, once a day with the long acting tiotropium.
	• Inhaled beta-sympathomimetic (salbutamol, terbutaline, fenoterol) [A]
	  • May be combined with an anticholinergic drug
	  • Long-acting beta-sympathomimetics (formoterol, salmeterol [B]) may improve quality of life and reduce symptoms [C].
	• Oral, long-acting theophylline [A]
	  • Adverse effects (central nervous system, gastrointestinal symptoms) are common (follow-up of serum concentrations is necessary)
	  • Arrhythmias and convulsions are signs of toxicity.
	  • Keep in mind various interactions with other drugs (e.g., antibiotics)

GOLD (2005)	Bronchodilator medications are central to the symptomatic management of COPD (Evidence A) (see Table 9 in the Executive Summary). They are given either on an as-needed basis for relief of persistent or worsening symptoms, or on a regular basis to prevent or reduce symptoms. Dose-response relationships using the FEV_1 as the outcome are relatively flat in all classes of bronchodilators. Side effects are pharmacologically predictable and dose-dependent. Adverse effects are less likely and resolve more rapidly after treatment withdrawal with inhaled than with oral treatment. When treatment is given by the inhaled

route, attention to effective drug delivery and training in inhaler technique is essential.

Bronchodilators drugs commonly used in treating COPD include:

Beta$_2$-agonists:

Short-acting

- Fenoterol
- Salbutamol (albuterol)
- Terbutaline

Long-acting

- Formoterol
- Salmeterol

Anticholinergics:

Short-acting

- Ipratropium bromide
- Oxitropium bromide

Long-acting

- Tiotropium

Methylxanthines:

- Aminophylline (slow release preparations)
- Theophylline (slow release preparations)

The choice depends on the availability of the medication and the patient's response. All categories of bronchodilators have been shown to increase exercise capacity in COPD, without necessarily producing significant changes in FEV_1 (Evidence A).

Regular treatment with long acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators, but more expensive (Evidence A).

Regular use of a long-acting beta$_2$-agonist or long-acting anticholinergic improves health status.

Theophylline is effective in COPD, but due to its potential toxicity, inhaled bronchodilators are preferred when available. All studies that have shown efficacy of theophylline in COPD were

	done with slow-release preparations.
NCCCC/NICE (2004)	Inhaled Bronchodilator Therapy B - Short-acting bronchodilators, as necessary, should be the initial empirical treatment for the relief of breathlessness and exercise limitation. D - The effectiveness of bronchodilator therapy should not be assessed by lung function alone but should include a variety of other measures such as improvement in symptoms, activities of daily living, exercise capacity, and rapidity of symptom relief. A - Patients who remain symptomatic should have their inhaled treatment intensified to include long-acting bronchodilators or combined therapy with a short-acting $beta_2$-agonist and a short-acting anticholinergic. A - Long-acting bronchodilators should be used in patients who remain symptomatic despite treatment with short-acting bronchodilators, because these drugs appear to have additional benefits over combinations of short-acting drugs. D - Long-acting bronchodilators should also be used in patients who have two or more exacerbations per year. D - The choice of drug(s) should take into account the patient's response to a trial of the drug, the drug's side effects, patient preference, and cost. Theophylline In this section, the term theophylline is used to mean long-acting/slow-release formulations of this drug. D - Theophylline should only be used after a trial of short-acting bronchodilators and long-acting bronchodilators, or in patients who are unable to use inhaled therapy, as there is a need to monitor plasma levels and interactions. D - Particular caution needs to be taken with the use of theophylline in elderly patients because of differences in pharmacokinetics, the increased likelihood of comorbidities, and the use of other medications. D - The effectiveness of the treatment with theophylline should be assessed by improvements in symptoms, activities of daily living, exercise capacity, and lung function.

	D - The dose of theophylline prescribed should be reduced at the time of an exacerbation if macrolide or fluoroquinolone antibiotics (or other drugs known to interact) are prescribed.
Corticosteroids (Anti-inflammatory Medication)	
FMS (2005)	Inhaled steroids are prescribed for patients with frequent exacerbations [B]. Oral steroids appear to improve lung function and symptoms more than placebo in stable COPD, but not all people benefit equally. Long-term use does not slow the decline in lung function and there is an increased risk of side-effects [B].
GOLD (2005)	Regular treatment with inhaled glucocorticosteroids does not modify the long-term decline in FEV_1 in patients with COPD. However, regular treatment with inhaled glucocorticosteroids is appropriate for symptomatic COPD patients with an FEV_1 <50% predicted (Stage III Severe COPD and Stage IV Very Severe COPD) and repeated exacerbations (for example, 3 in the last three years) (Evidence A). This treatment has been shown to reduce the frequency of exacerbations and thus improve health status (Evidence A), and withdrawal from treatment with inhaled glucocorticosteroids can lead to exacerbations in some patients. Inhaled glucocorticosteroid combined with a long-acting $beta_2$-agonist is more effective than the individual components (Evidence A). Short-term treatment with a combined inhaled glucocorticosteroid and long-acting $beta_2$-agonist resulted in greater control of lung function and symptoms than combined antocholinergic and short-acting $beta_2$-agonist. Many existing COPD guidelines recommend the use of a short course (two weeks) of oral glucocorticosteroids to identify COPD patients who might benefit from long-term treatment with oral or inhaled glucocorticosteroids. There is mounting evidence, however, that a short course of oral glucocorticosteroids is a poor predictor of the long-term response to inhaled glucocorticosteroids in COPD. Long-term treatment with oral glucocorticosteroids is not recommended in COPD (Evidence A). There is no evidence of long-term benefit from this treatment. Moreover, a side effect of long-term treatment with systemic glucocorticosteroids is steroid myopathy, which contributes to muscle weakness, decreased functionality, and respiratory failure in patients with advanced COPD. Glucocorticosteroid drugs used in treating COPD include:

	Inhaled glucocorticosteroids • Beclomethasone • Budesonide • Fluticasone • Triamcinolone Systemic glucocorticosteroids • Prednisone • Methyl-prednisone
NCCCC/NICE (2004)	Inhaled Corticosteroids None of the inhaled corticosteroids currently available are licensed for use alone in the treatment of COPD. The following recommendations therefore include usage outside licensed indications, and prescribers need to remember that responsibility for such prescribing lies with them. A - Oral corticosteroid reversibility tests do not predict response to inhaled corticosteroid therapy and should not be used to identify which patients should be prescribed inhaled corticosteroids. B - Inhaled corticosteroids should be prescribed for patients with an FEV_1 less than or equal to 50% predicted, who are having two or more exacerbations requiring treatment with antibiotics or oral corticosteroids in a 12-month period. The aim of treatment is to reduce exacerbation rates and slow the decline in health status and not to improve lung function per se. D - Clinicians should be aware of the potential risk of developing osteoporosis and other side effects in patients treated with high-dose inhaled corticosteroids (especially in the presence of other risk factors), and should discuss the risk with patients. Oral Corticosteroids D - Maintenance use of oral corticosteroid therapy in COPD is not normally recommended. Some patients with advanced COPD may require maintenance oral corticosteroids when these cannot be withdrawn following an exacerbation. In these cases, the dose of oral corticosteroids should be kept as low as possible. D - Patients treated with long-term oral corticosteroid therapy should be monitored for the development of osteoporosis and given appropriate prophylaxis. Patients over the age of 65 should be started on prophylactic treatment, without monitoring.

Combination Therapy	
FMS (2005)	With continuous symptoms (FEV_1 generally <50% predicted) • Anticholinergics and short-acting beta-2-agonists (combined) according to clinical response or • Long acting anticholinergic or beta-2-agonist, or their combination
GOLD (2005)	Combining drugs with different mechanisms and durations of action might increase the degree of bronchodilation for equivalent or lesser side effects. A combination of a short-acting $beta_2$-agonist and an anticholinergic produces greater and more sustained improvements in FEV_1 than either alone and does not produce evidence of tachyphylaxis over 90 days of treatment (Evidence A). Combination of a $beta_2$-agonist, an anticholinergic and/or theophylline may produce additional improvements in lung function and health status. Increasing the number of drugs usually increases costs, and an equivalent benefit may occur by increasing the dose of one bronchodilator when side effects are not a limiting factor. Detailed assessments of this approach have not been carried out. Combination drugs used in treating COPD include: <u>Combination short-acting $beta_2$-agonists plus anticholinergic in one inhaler</u> • Fenoterol/Ipratropium • Salbutamol/Ipratropium <u>Combination long-acting $beta_2$-agonists plus glucocorticosteroids in one inhaler</u> • Formoterol/Budesonide • Salmeterol/Fluticasone
NCCCC/NICE (2004)	A - If patients remain symptomatic on monotherapy, their treatment should be intensified by combining therapies from different drug classes. Effective combinations include: • $Beta_2$-agonist and anticholinergic • $Beta_2$-agonist and theophylline • Anticholinergic and theophylline

	• Long-acting beta$_2$-agonist and inhaled corticosteroids D - The clinical effectiveness of combined treatments can be assessed by improvements in symptoms, activities of daily living, exercise capacity, and lung function. Combination treatment should be discontinued if there is no benefit after 4 weeks.
OTHER PHARMACOLOGIC TREATMENTS	
Vaccines	
FMS (2005)	• Influenza vaccination should be given yearly to all patients with clearly decreased ventilatory function [C]. • Pneumococcal vaccination is recommended. • Haemophilus influenzae vaccination may also be beneficial [B].
GOLD (2005)	Influenza vaccines can reduce serious illness and death in COPD patients by about 50%. Vaccines containing killed or live, inactivated viruses are recommended and should be given once (in autumn) or twice (in autumn and winter) each year (Evidence A). A pneumococcal vaccine containing 23 virulent serotypes has been used but sufficient data to support its general use in COPD patients are lacking (Evidence B).
NCCCC/NICE (2004)	HSC - Pneumococcal vaccination and an annual influenza vaccination should be offered to all patients with COPD as recommended by the Chief Medical Officer. (Evidence from Health Service Circulars [HSC]) NICE - "Within their licensed indications, zanamivir and oseltamivir are recommended for the treatment of at-risk adults who present with influenza-like illness and who can start therapy within 48 hours of the onset of symptoms." (NICE technology appraisal guidance- No. 58. 2003) (Evidence from NICE guidelines or Health Technology Appraisal Program) The technology appraisal also notes that zanamivir should be used with caution in people with COPD because of risk of bronchospasm. If people with COPD are prescribed zanamivir, they should be made aware of the risks and have a fast-acting bronchodilator available.
Alpha-1 Antitrypsin Augmentation Therapy	
FMS (2005)	No recommendations offered.

GOLD (2005)	Young patients with severe hereditary alpha-1 antitrypsin deficiency and established emphysema may be candidates for alpha-1 antitrypsin augmentation therapy. However, this therapy is very expensive, is not available in most countries, and is not recommended for COPD that is unrelated to alpha-1 antitrypsin deficiency (Evidence C).
NCCCC/NICE (2004)	D - Patients identified as having alpha-1 antitrypsin deficiency should be offered the opportunity to be referred to a specialist centre to discuss the clinical management of this condition. D - Alpha-1 antitrypsin replacement therapy is not recommended in the management of patients with alpha-1 antitrypsin deficiency
Antibiotics	
FMS (2005)	Antibiotics have no place in the basic maintenance therapy of COPD.
GOLD (2005)	The use of antibiotics, other than in treating infectious exacerbations of COPD and other bacterial infections, is not recommended (Evidence A).
NCCCC/NICE (2004)	D - There is insufficient evidence to recommend prophylactic antibiotic therapy in the management of stable COPD.
Mucolytic Therapy	
FMS (2005)	Mucolytic agents should be used only temporarily [B].
GOLD (2005)	Mucolytic (Mucokinetic, Mucoregulator) Agents: (ambroxol, erdosteine, carbocysteine, iodinated glycerol): Although a few patients with viscous sputum may benefit from mucolytics, the overall benefits seem to be very small. Therefore, the widespread use of these agents cannot be recommended on the basis of the present evidence (Evidence D).
NCCCC/NICE (2004)	B - Mucolytic drug therapy should be considered in patients with a chronic cough productive of sputum. D - Mucolytic therapy should be continued if there is symptomatic improvement (for example, reduction in frequency of cough and sputum production).
Antioxidant Agents	
FMS	No recommendations offered.

(2005)	
GOLD (2005)	Antioxidants, in particular N-acetylcysteine, have been shown to reduce the frequency of exacerbations and could have a role in the treatment of patients with recurrent exacerbations (Evidence B). However, before their routine use can be recommended, the results of ongoing trials will have to be carefully evaluated.
NCCCC/NICE (2004)	A - Treatment with alpha-tocopherol and beta-carotene supplements, alone or in combination, is not recommended.
Antitussives	
FMS (2005)	No recommendations offered
GOLD (2005)	Cough, although sometimes a troublesome symptom in COPD, has a significant protective role. Thus, the regular use of antitussives is contraindicated in stable COPD (Evidence D).
NCCCC/NICE (2004)	D - Antitussive therapy should not be used in the management of stable COPD.
NON-PHARMACOLOGIC TREATMENTS	
Long-term Oxygen Therapy (LTOT)	
FMS (2005)	<u>Oxygen Therapy at Home</u> Basics • Oxygen therapy at home can be used to prevent elevation of pulmonary arterial pressure in advanced COPD and to extend the survival of the patient. • The effect of oxygen therapy on symptoms (e.g., shortness of breath) is quite limited. • Oxygen therapy at home is meant only for patients with chronic hypoxaemia (i.e., arterial desaturation). • Treatment decisions should be made after critical consideration. • When initiating oxygen therapy at home, appropriate monitoring of treatment must be ensured. Treatment decisions and implementation of treatment are best left to a local pulmonary clinic to be taken care of. Initiation Criteria for Oxygen Therapy • Chronic, advanced pulmonary disease (FEV_1 <1.5 L)

	• The partial pressure of oxygen in arterial blood, measured with the patient in a stable phase of the disease breathing room air <7.3 kPa in two samples taken with an interval of at least three weeks.
	• Partial pressure of oxygen can also be 7.3 to 8.0 kPa if one of the following criteria is involved:
	  • Signs of increased pulmonary arterial pressure (e.g., oedema)
	  • Secondary polycythaemia (haematocrit >55)
	  • Significant nocturnal hypoxaemia established by oximetry and reversible by oxygen therapy and not caused by concomitant sleep apnoea syndrome
	  • Significant neuropsychological symptoms reversible by oxygen therapy
	• Oxygen therapy gives the desired response (PaO_2 >8.0 kPa) without unfavourable increase in the partial pressure of carbon dioxide in arterial blood.
	• The patient does not smoke and is sufficiently co-operative.
	
	Implementation of Treatment
	
	• Oxygen therapy at home is implemented in most cases using an electric oxygen concentrator. The oxygen concentrator eliminates nitrogen from room air and provides the patient with over 90%-proof oxygen.
	• Portable liquid oxygen is suitable for a minority of patients. Primarily these are patients who are in the working life and/or who are motivated for rehabilitation through physical exercise.
	• All oxygen therapy necessitates good co-operation by the patient and willingness for long-term co-operation with the treating unit.
	• Home calls made by a rehabilitation instructor are an essential part of the monitoring of patients receiving oxygen therapy at home.

GOLD (2005)	LTOT is generally introduced in Stage IV: Very Severe Chronic Obstructive Pulmonary Disease for patients who have: • PaO_2 at or below 7.3 kPa (55 mm Hg) or SaO_2 at or below 88%, with or without hypercapnia; or • PaO_2 between 7.3 kPa (55 mm Hg) and 8.0 kPa (60 mm Hg) or SaO_2 89%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive heart failure, or polycythemia (hematocrit >55%). The goal of LTOT is to increase the baseline PaO_2 to at least 8.0 kPa (60 mm Hg) at sea level and rest, and/or produce SaO_2 at least 90%, which will preserve vital organ function by ensuring

	an adequate delivery of oxygen. A decision about the use of LTOT should be based on the waking PaO_2 values. The prescription should always include the source of supplemental oxygen (gas or liquid), the method of delivery, duration of use, and the flow rate at rest, during exercise, and during sleep.
NCCCC/NICE (2004)	Long-term Oxygen Therapy (LTOT) C - Clinicians should be aware that inappropriate oxygen therapy in people with COPD may cause respiratory depression. A - LTOT is indicated in patients with COPD who have a PaO_2 less than 7.3 kPa when stable or a PaO_2 greater than 7.3 and less than 8 kPa when stable and one of: secondary polycythaemia, nocturnal hypoxaemia (oxygen saturation of arterial blood [SaO_2] less than 90% for more than 30% of time), peripheral oedema, or pulmonary hypertension. A - To get the benefits of LTOT patients should breathe supplemental oxygen for at least 15 hours per day. Greater benefits are seen in patients receiving oxygen for 20 hours per day. D - The need for oxygen therapy should be assessed in: • All patients with severe airflow obstruction (FEV_1 less than 30% predicted) • Patients with cyanosis • Patients with polycythaemia • Patients with peripheral oedema • Patients with a raised jugular venous pressure • Patients with oxygen saturations less than or equal to 92% breathing air Assessment should also be considered in patients with moderate airflow obstruction (FEV_1 30 to 49% predicted). D - To ensure all patients eligible for LTOT are identified, pulse oximetry should be available in all healthcare settings. D - The assessment of patients for LTOT should comprise the measurement of arterial blood gasses on two occasions at least 3 weeks apart in patients who have a confident diagnosis of COPD, who are receiving optimum medical management, and whose COPD is stable. D - Patients receiving LTOT should be reviewed at least once per year by practitioners familiar with LTOT, and this review should

include pulse oximetry.

D - Oxygen concentrators should be used to provide the fixed supply at home for long-term oxygen therapy.

D - Patients should be warned about the risks of fire and explosion if they continue to smoke when prescribed oxygen.

Ambulatory Oxygen Therapy

D - People who are already on LTOT who wish to continue with oxygen therapy outside the home, and who are prepared to use it, should have ambulatory oxygen prescribed.

D - Ambulatory oxygen therapy should be considered in patients who have exercise desaturation, are shown to have an improvement in exercise capacity and/or dyspnoea with oxygen, and have the motivation to use oxygen.

D - Ambulatory oxygen therapy is not recommended in COPD if PaO_2 is greater than 7.3 kPa and there is no exercise desaturation.

D - Ambulatory oxygen therapy should only be prescribed after an appropriate assessment has been performed by a specialist. The purpose of the assessment is to assess the extent of desaturation, the improvement in exercise capacity with supplemental oxygen, and the oxygen flow rate required to correct desaturation, aiming to keep the SaO_2 above 90%.

D - Small light-weight cylinders, oxygen-conserving devices, and portable liquid oxygen systems should be available for the treatment of patients with COPD.

D - A choice about the nature of equipment prescribed should take account of the hours of ambulatory oxygen use required by the patient and the oxygen flow rate required. (See Table 12 in the original guideline document for a list of appropriate equipment for ambulatory oxygen therapy.)

Short-burst Oxygen Therapy

C - Short-burst oxygen therapy should only be considered for episodes of severe breathlessness in patients with COPD not relieved by other treatments.

D - Short-burst oxygen therapy should only continue to be prescribed if an improvement in breathlessness following therapy has been documented.

	D - When indicated, short-burst oxygen should be provided from cylinders.
Smoking Prevention/Smoking Cessation	
FMS (2005)	A "Basic Rule" of the guideline is the promotion of smoking cessation. Cessation of Smoking • The most essential factor regarding the prognosis • Does not normalize lung function, but the progressive deterioration of FEV_1 slows down and proceeds at the same pace as in nonsmokers. • According to present knowledge, there is no drug therapy available that could delay the deterioration of lung function if the patient continues smoking. Drugs useful only for relieving subjective symptoms and in the treatment of acute exacerbations.
GOLD (2005)	• Reduction of total personal exposure to tobacco smoke, occupational dusts, and chemicals, and indoor and outdoor air pollutants are important goals to prevent the onset and progression of COPD. • Smoking cessation is the single most effective and cost-effective intervention to reduce the risk of developing COPD and stop its progression (Evidence A). • Brief tobacco dependence treatment is effective (Evidence A) and every tobacco user should be offered at least this treatment at every visit to the health care provider. • Three types of counseling are especially effective: practical counseling, social support as part of treatment, and social support arranged outside of treatment (Evidence A). • Several effective pharmacotherapies for tobacco dependence are available (Evidence A), and at least one of these medications should be added to counseling if necessary and in the absence of contraindications. Smoking Prevention and Cessation Comprehensive tobacco control policies and programs with clear, consistent, and repeated nonsmoking messages should be delivered through every feasible channel. Legislation to establish smoke-free schools, public facilities, and work environments should be encouraged by government officials, public health workers, and the public. Smoking cessation is the single most effective and cost-effective way to reduce the risk of developing COPD and stop its

	progression. Even a brief, three-minute period of counseling to urge a smoker to quit can be effective, and at the very least this should be done for every smoker at every visit. Health education, public policy, and information dissemination programs are all vital components in a comprehensive cessation effort. Guidelines for Smoking Cessation: Guidelines for smoking cessation were published by the United States Agency for Health Care Policy and Research (AHCPR) (now the Agency for Healthcare Research and Quality [AHRQ] in 1996 and updated in 2000 by the United States Public Health Service in the publication titled "Treating Tobacco Use and Dependence: A Clinical Practice Guideline." Smoking Cessation Intervention Process: The Public Health Service Report recommends a five-step program for intervention, which provides a strategic framework helpful to health care providers interested in helping their patients stop smoking. Three types of counseling are especially effective: (1) practical counseling, (2) social support as part of treatment, and (3) social support arranged outside of treatment. Pharmacotherapy: Numerous effective pharmacotherapies for smoking cessation now exist. Except in the presence of special circumstances, pharmacotherapy is recommended when counseling is not sufficient to help patients quit smoking. Special consideration should be given before using pharmacotherapy in selected populations: people with medical contraindications, light smokers fewer than 10 cigarettes/day, and pregnant and adolescent smokers. (Refer to the original guideline for specific recommendations regarding pharmacotherapy.)
NCCCC/NICE (2004)	D - An up-to-date smoking history, including pack years smoked (number of cigarettes smoked per day, divided by 20, multiplied by the number of years smoked), should be documented for everyone with COPD. A - All COPD patents still smoking, regardless of age, should be encouraged to stop, and offered help to do so, at every opportunity. B - Unless contraindicated, bupropion or nicotine replacement therapy (NRT) combined with an appropriate support programme should be used to optimise smoking quit rates for people with COPD. NICE - NICE Technology Appraisal Guidance No 39 (see Section 6 of the original guideline document) recommends: "If a smoker's attempt to quit is unsuccessful with treatment

	using either nicotine replacement therapy or bupropion, the National Health Service should normally fund no further attempts within 6 months. However, if external factors interfere with a person's initial attempt to stop smoking, it may be reasonable to try again sooner."
PATIENT EDUCATION	
FMS (2005)	No recommendations offered
GOLD (2005)	• For patients with COPD, health education can play a role in improving skills, ability to cope with illness, and health status. It is effective in accomplishing certain goals, including smoking cessation (Evidence A). Although patient education alone does not improve exercise performance or lung function, it can play a role in improving skills, ability to cope with illness, and health status. In addition, patient education is effective in accomplishing certain specific goals, including smoking cessation, initiating discussions and understanding of advanced directives and end-of-life issues, and improving patient responses to acute exacerbations. Education may take place in many settings: consultations with physicians or other health care workers, home care or outreach programs, and comprehensive pulmonary rehabilitation programs. It should be tailored to the needs and environment of the patient, interactive, directed at improving quality of life, simple to follow, practical, and appropriate to the intellectual and social skills of the patient and the caregiver. The topics that seem most appropriate for an education program to cover include: smoking cessation; basic information about chronic obstructive pulmonary disease and pathophysiology of the disease; general approach to therapy and specific aspects of medical treatment; self-management skills; strategies to help minimize dyspnea; advice about when to seek help; self-management and decision-making in exacerbations; and advance directives and end-of-life issues. Topics for Patient Education: Stage 0: At Risk • Information and advice about reducing risk factors Stage I: Mild COPD through Stage III: Severe COPD Above topic, plus:

	• Information about the nature of COPD • Instruction on how to use inhalers and other treatments • Recognition and treatment of exacerbations • Strategies for minimizing dyspnea Stage IV: Very Severe COPD Above topics, plus: • Information about complications • Information about oxygen treatment • Advance directives and end-of-life decisions

NCCCC/NICE (2004)	A - There are significant differences in the response of patients with COPD and asthma to education programmes. Programmes designed for asthma should not be used in COPD.
	
	D - Specific educational packages should be developed for patients with COPD.
	
	• Suggested topics for inclusion are:
	  • disease education (anatomy, physiology, pathology and pharmacology, including oxygen therapy & vaccination)
	  • dyspnea/symptom management, including chest clearance techniques
	  • smoking cessation
	  • energy conservation/pacing
	  • nutritional advice
	  • managing travel
	  • benefits system and disabled parking badges
	  • advance directives (living wills)
	  • making a change plan
	  • anxiety management
	  • goal setting and rewards
	  • relaxation
	  • identifying and changing beliefs about exercise and health related behaviors
	  • loving relationships/sexuality
	  • exacerbation management (including when to seek help, self-management and decision making, coping with setbacks and relapses)
	  • home care support
	  • managing surgery (non thoracic)
	  • the benefits of physical exercise
	  • support groups
	• The packages should take account of the different needs of patients at different stages of their disease.

	D - Patients with moderate and severe COPD should be made aware of the technique of non-invasive ventilation (NIV). Its benefits and limitations should be explained so that, if it is ever necessary in the future, they will be aware of these issues.
Surgery	
FMS (2005)	Surgery (bullectomy, lung transplantation, lung volume reduction) can be recommended only to a small subset of the patients after careful evaluation. Stapling is more effective than laser resection for lung volume reduction in diffuse emphysema, but there is no evidence from randomized trials comparing surgery with optimal conservative treatment [B].
GOLD (2005)	Bullectomy: In carefully selected patients, this procedure is effective in reducing dyspnea and improving lung function (Evidence C). A thoracic computed tomography scan, arterial blood gas measurement, and comprehensive respiratory function tests are essential before making a decision regarding a patient's suitability for resection of a bulla. Lung Volume Reduction Surgery (LVRS): LVRS is a surgical procedure in which parts of the lung are resected to reduce hyperinflation. LVRS does not improve life expectancy but improves exercise capacity in patients with predominant upper lobe emphysema and a low post-rehabilitation exercise capacity, and may improve global health status in patients with heterogeneous emphysema. In some centers, with adequate experience, perioperative mortality of LVRS has been reported to be less than 5%. However, hospital costs associated with LVRS are high and it remains an experimental palliative surgical procedure not recommended for widespread use. Lung Transplantation: In appropriately selected patients with very advanced COPD, lung transplantation has been shown to improve quality of life and functional capacity (Evidence C). Criteria for referral for lung transplantation include FEV_1 <35% predicted, PaO_2 <7.3 to 8.0 kPa (55 to 60 mm Hg), $PaCO_2$ >6.7 kPa (50 mm Hg), and secondary pulmonary hypertension.
NCCCC/NICE (2004)	C - Patients who are breathless and have a single large bulla on a computed tomography (CT) scan and an FEV_1 less than 50% predicted should be referred for consideration of bullectomy. A - Patients with severe COPD who remain breathless with marked restrictions of their activities of daily living, despite maximal medical therapy (including rehabilitation), should be referred for consideration of lung volume reduction surgery if

	they meet all of the following criteria: • FEV_1 more than 20% predicted • $PaCO_2$ less than 7.3 kPa • Upper lobe predominant emphysema • T_LCO more than 20% predicted C - Patients with severe COPD who remain breathless with marked restrictions of their activities of daily living despite maximal medical therapy should be considered for referral for assessment for lung transplantation, bearing in mind comorbidities and local surgical protocols. Considerations include: • Age • FEV_1 • $PaCO_2$ • Homogeneously distributed emphysema on CT scan • Elevated pulmonary artery pressures with progressive deterioration
ONGOING ASSESSMENT AND FOLLOW-UP	
FMS (2005)	No recommendations offered.
GOLD (2005)	Monitoring Disease Progression and Development of Complications: COPD is usually a progressive disease, and a patient's lung function can be expected to worsen over time, even with the best available care. Symptoms and objective measures of airflow limitation should be monitored for development of complications and to determine when to adjust therapy. Follow-up visits should include a discussion of new or worsening symptoms. Spirometry should be performed if there is a substantial increase in symptoms or a complication. Measurement of arterial blood gas tensions should be considered in all patients with an FEV_1 <40% predicted or clinical signs of respiratory failure or right heart failure. Elevation of the jugular venous pressure and the presence of pitting ankle edema are often the most useful findings suggestive of right heart failure in clinical practice. Measurement of pulmonary arterial pressure is not recommended in clinical practice as it does not add practical information beyond that obtained from a knowledge of PaO_2. Monitor Pharmacotherapy and Other Medical Treatment: In order to adjust therapy appropriately as the disease progresses, each follow-up visit should include a discussion of the current

	therapeutic regimen. Dosages of various medications, adherence to the regimen, inhaler technique, effectiveness of the current regime at controlling symptoms, and side effects of treatment should be monitored. Monitor Exacerbation History: Frequency, severity, and likely causes of exacerbations should be evaluated. Increased sputum volume, acutely worsening dyspnea, and the presence of purulent sputum should be noted. Severity can be estimated by the increased need for bronchodilator medication or glucocorticosteroids and by the need for antibiotic treatment. Hospitalizations should be documented, including the facility, duration of stay, and any use of critical care or intubation. Monitor Comorbidities: In treating patients with chronic obstructive pulmonary disease, it is important to consider the presence of concomitant conditions such as bronchial carcinoma, tuberculosis, sleep apnea, and left heart failure. The appropriate diagnostic tools (chest x-ray, electrocardiogram, etc.) should be used whenever symptoms (e.g., hemoptysis) suggest one of these conditions.

NCCCC/NICE (2004)	D - Follow-up of all patients with COPD should include:
	
	• Highlighting the diagnosis of COPD in the case record and recording this using Read codes on a computer database
	• Recording the values of spirometric tests performed at diagnosis (both absolute and percent predicted)
	• Offering smoking cessation advice
	• Recording the opportunistic measurement of spirometric parameters (a loss of 500 mL or more over 5 years will select out those patients with rapidly progressing disease who may need specialist referral and investigation)
	
	D - Patients with mild or moderate COPD should be reviewed at least once per year, or more frequently if indicated, and the review should cover the issues listed below and in Table 14 of the original guideline document.
	
	• Clinical assessment
	  • smoking status & desire to quit
	  • adequacy of symptom control
	  • breathlessness
	  • exercise tolerance
	  • estimated exacerbation frequency
	  • presence of complications
	  • effects of each drug treatment
	  • inhaler technique
	  • need for referral to specialist and therapy services
	  • need for pulmonary rehabilitation
	• Measurements to make

	• FEV_1 & FVC
	• BMI
	• MRC dyspnoea score
	
	D - For most patients with stable severe disease, regular hospital review is not necessary, but there should be locally agreed mechanisms to allow rapid access to hospital assessment when necessary
	
	D - When patients with severe COPD are reviewed in primary care, they should be seen at least twice a year, and specific attention should be paid to the issues listed below and in Table 14 of the original guideline document:
	
	• Clinical assessment
	  • smoking status & desire to quit
	  • adequacy of symptom control
	  • breathlessness
	  • exercise tolerance
	  • estimated exacerbation frequency
	  • presence of cor pulmonale
	  • need for long-term oxygen therapy
	  • patient's nutritional state
	  • presence of depression
	  • effects of each drug treatment
	  • inhaler technique
	  • need for Social Services & Occupational Therapy input
	  • need for referral to specialist and therapy services
	  • need for pulmonary rehabilitation
	• Measurements to make
	  • FEV_1 & FVC
	  • BMI
	  • MRC dyspnoea score
	  • SaO_2
	
	D - Patients with severe disease requiring interventions such as long-term noninvasive ventilation should be reviewed regularly by specialists.

TABLE 3: BENEFITS AND HARMS	
Benefits	
FMS (2005)	Appropriate management and treatment of COPD may help relieve patient symptoms, improve exercise capacity, improve lung function, reduce morbidity and mortality, improve quality of life, and reduce frequency and severity of exacerbations.

GOLD (2005)	Overall Benefits of Guideline Recommendations
	
	• The goals of effective COPD management are to:
	  • Prevent disease progression
	  • Relieve symptoms
	  • Improve exercise tolerance
	  • Improve health status
	  • Prevent and treat complications
	  • Prevent and treat exacerbations
	  • Reduce mortality
	• COPD prevention
	
	Long-term Oxygen Therapy
	
	The long-term administration of oxygen (>15 hours per day) to patients with chronic respiratory failure has been shown to increase survival. It can also have a beneficial impact on hemodynamics, hematologic characteristics, exercise capacity, lung mechanics, and mental state.
	
	Smoking cessation is the single most effective and cost-effective way to reduce the risk of developing COPD and stop its progression.

NCCCC/NICE (2004)	If adopted, the guideline recommendations should lead to better standards of care and thus better outcomes from chronic obstructive pulmonary disease.
Harms	
FMS (2005)	• Common adverse effects of oral, long-acting theophylline include central nervous system and gastrointestinal symptoms. Arrhythmias and convulsions are signs of toxicity. • Adverse drug reactions of ipratropium bromide included dry mouth and tremor.
GOLD (2005)	Beta$_2$-agonists: Stimulation of beta$_2$-receptors can produce resting sinus tachycardia and has the potential to precipitate cardiac rhythm disturbances in very susceptible patients, although this appears to be a remarkably rare event with inhaled therapy. Exaggerated somatic tremor is troublesome in some older patients treated with higher doses of beta$_2$-agonists, whatever the route of administration, and this limits the dose that can be tolerated. Although hypokalemia can occur, especially when treatment is combined with thiazide diuretics, and oxygen consumption can be increased under resting conditions, these metabolic effects

	show tachyphylaxis unlike the bronchodilator actions. Mild falls in PaO_2 occur after administration of both short- and long-acting $beta_2$-agonists, but the clinical significance of these changes is doubtful. Despite the concerns raised some years ago, further detailed study has found no association between $beta_2$-agonist use and an accelerated loss of lung function or increased mortality in chronic obstructive pulmonary disease. Anticholinergics: Anticholinergic drugs, such as ipratropium bromide, are poorly absorbed, which limits the troublesome systemic effects seen with atropine. Extensive use of this class of inhaled agents in a wide range of doses and clinical settings has shown them to be very safe. The main side effect is dryness of the mouth. Twenty-one days of inhaled tiotropium, 18 micrograms a day as a dry powder, does not retard mucus clearance from the lungs. Although occasional prostatic symptoms have been reported, there are no data to prove a true causal relationship. A bitter, metallic taste is reported by some patients using ipratropium. An unexpected small increase in cardiovascular events in COPD patients regularly treated with ipratropium bromide has been reported and required further investigation. Methylxanthines: Toxicity is dose related, a particular problem with the xanthine derivatives because their therapeutic ratio is small and most of the benefit occurs only when near-toxic doses are given. Methylxanthines are nonspecific inhibitors of all phosphodiesterase enzyme subsets, which explains their wide range of toxic effects. Problems include the development of atrial and ventricular arrhythmias (which can prove fatal) and grand mal convulsions (which can occur irrespective of prior epileptic history). More common and less dramatic side effects include headaches, insomnia, nausea, and heartburn, and these may occur within the therapeutic range of serum theophylline. Unlike the other bronchodilator classes, xanthine derivatives may involve a risk of overdose (either intentional or accidental). Oral Glucocorticosteroids: A side effect of long-term treatment with systemic glucocorticosteroids is steroid myopathy, which contributes to muscle weakness, decreased functionality, and respiratory failure in subjects with advanced chronic obstructive pulmonary disease.
NCCCC/NICE (2004)	• Particular caution needs to be taken with the use of theophylline in elderly patients because of differences in pharmacokinetics, the increased likelihood of comorbidities, and the use of other medications. • Clinicians should be aware of the potential risk of developing osteoporosis and other side effects in patients treated with high-dose inhaled corticosteroids (especially in the presence of other risk factors) and should discuss the risk with

	patients. • Patients should be warned about the risks of fire and explosion if they continue to smoke when prescribed oxygen. • The technology appraisal also notes that zanamivir should be used with caution in people with COPD because of risk of bronchospasm. If people with COPD are prescribed zanamivir they should be made aware of the risks and have a fast-acting bronchodilator available. • Care should be taken when using intravenous theophylline because of interactions with other drugs and potential toxicity if the patient has been on oral theophylline.

TABLE 4: EVIDENCE AND RECOMMENDATION RATING SCHEMES	
FMS (2005)	Levels of Evidence A. Strong research-based evidence. Multiple relevant, high-quality scientific studies with homogeneous results. B. Moderate research-based evidence. At least one relevant, high-quality study or multiple adequate studies. C. Limited research-based evidence. At least one adequate scientific study. D. No research-based evidence. Expert panel evaluation of other information.
GOLD (2005)	Levels of Evidence A. Randomized controlled trials. Rich body of data. Definition: Evidence is from endpoints of well-designed randomized controlled trials that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants. B. Randomized controlled trials. Limited data. Definition: Evidence is from endpoints of intervention studies that include only a limited number of patients, posthoc or subgroup analysis of randomized controlled trials, or meta-analysis of randomized controlled trials. In general, Category B pertains when few randomized trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent. C. Nonrandomized trials. Observational studies. Definition: Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies.

	D. Panel consensus. Judgment. Definition: This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was deemed insufficient to justify placement in one of the other categories. The Panel Consensus is based on clinical experience or knowledge that does not meet the above-listed criteria.
NCCCC/NICE (2004)	Levels of Evidence Ia: Evidence from systematic reviews or meta-analysis of randomised controlled trials Ib: Evidence from at least one randomised controlled trial IIa: Evidence from at least one controlled study without randomisation IIb: Evidence from at least one other type of quasi-experimental study III: Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies IV: Evidence from expert committee reports or opinions and/or clinical experience of respected authorities NICE: Evidence from NICE guidelines or Health Technology Appraisal Programme HSC: Evidence from Health Service Circulars Grading of Recommendations A. Based on hierarchy I evidence B. Based on hierarchy II evidence or extrapolated from hierarchy I evidence C. Based on hierarchy III evidence or extrapolated from hierarchy I or II evidence D. Directly based on hierarchy IV evidence or extrapolated from hierarchy I, II, or III evidence

The Finnish Medical Society Duodecim (FMS), the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (a collaborative project of the World Health Organization/and National Heart, Lung, and Blood Institute), and the National Collaborating Centre for Chronic Conditions (a collaborating center for the National Institute for Health and Clinical Excellence [NCCCC/NICE]) present recommendations for the diagnosis and management of stable COPD and provide explicit reasoning behind their judgments. All three guidelines identify the type of supporting evidence for selected recommendations.

As mentioned in the introduction, there are some differences in the scope and format of the guidelines. The GOLD guideline differs from the other two guidelines in its global perspective and in its emphasis on prevention strategies. This guideline presents a COPD management plan with four components: (1) assessment and monitoring of disease, (2) reduction of risk factors, (3) management of stable COPD, and (4) management of exacerbations. Both the GOLD and NCCCC/NICE guidelines also differ from the FMS guideline by including recommendations for pulmonary rehabilitation which are addressed in Part III of this synthesis (currently under development).

Areas of Agreement

Definition of COPD

The three guidelines generally agree on the definition of COPD. Specifically, they agree that the disease is characterized by airflow limitation or obstruction, and that COPD is a progressive disease that is not fully reversible.

Differential Diagnosis

All three guidelines note that the primary differential diagnosis for COPD is asthma.

Physical Examination

The three guidelines generally agree that physical examination is rarely diagnostic in COPD.

Spirometry

The three guidelines agree on the importance of early spirometry to assess airflow limitation and aid in diagnosis of COPD.

Assessing Severity of Disease

The guidelines each recommend staging systems based on FEV_1 values for degree of severity (although the values and classification schemes vary among guidelines). All guidelines generally agree that the purpose for assessing severity is for prognostic and/or therapeutic purposes. In addition, all three guidelines remark on the importance of considering other factors (i.e., signs, symptoms, complications) in addition to FEV_1 values in assessing severity of disease. GOLD points out that the FEV_1 cutpoints are used for the purposes of simplicity and are

not clinically validated and may overestimate the prevalence of COPD in some groups, such as the elderly. Similarly, NCCCC/NICE cautions against use of spirometry alone to classify severity of the disease because the results may underestimate the impact of the disease in some patients and overestimate it in others.

Chest X-ray

All of the guidelines agree that chest x-ray is of limited value in the diagnosis of COPD. However, GOLD and NCCCC/NICE recommend chest x-ray to exclude other possible disease.

Measurement of Arterial Blood Gases (ABG)/Oximetry

All of the guidelines agree that blood gas analysis is an appropriate investigation for advanced COPD, and according to NCCCC/NICE to assess the need for oxygen therapy.

Measurement of Alpha-1 Antitrypsin (AAT) Levels

GOLD and NCCCC/NICE recommend measurement of AAT levels in patients with early onset COPD and a family history. The FMS guideline does not specifically recommend testing for AAT level, but they note that deficiency of AAT is a rare cause of emphysema in young patients.

Overall Management Strategy and General Approach to Pharmacologic Therapy

The guidelines are in general agreement that a stepped approach to treatment should be used, with therapy based on severity of symptoms and coexisting conditions.

Bronchodilators

All of the guidelines generally agree on the use and efficacy of various types of bronchodilating drugs. Short-acting or long-acting $beta_2$-agonists and anticholinergics, alone or in combination, are recommended for symptom control.

There is general agreement that short-acting bronchodilators, including short-acting $beta_2$- agonists, are appropriate as an initial treatment for relief of symptoms.

Theophylline

All guidelines agree that methylxanthines should not be used routinely or as a first line treatment. Caution is advised due to the potential toxicity of the drugs.

Corticosteroids

All of the guidelines generally agree that corticosteroids have limited or no long-term positive effect on lung function. However, two of the guidelines (GOLD and NCCCC/NICE) recommend use of inhaled corticosteroids in qualifying patients in

order to reduce frequency of exacerbations and improve health status or slow the decline in health status.

Vaccines

All of the guidelines recommend influenza vaccination in COPD patients. FMS and NCCCC/NICE recommend pneumococcal vaccination. GOLD acknowledges use of pneumococcal vaccine but states there is insufficient data to support its general use in COPD patients. They do not recommend against its use.

Alpha-1 Antitrypsin Augmentation Therapy

While FMS does not offer recommendations regarding this therapy, GOLD and NCCCC/NICE generally agree that the therapy may be appropriate for qualifying individuals.

Antibiotics

GOLD and NCCCC/NICE do not recommend prophylactic use of antibiotics in stable COPD. FMS does not address the use of antibiotics in stable COPD.

Mucolytic Therapy

There is general agreement that mucolytic therapy, while not used routinely, is appropriate at times in stable COPD patients. FMS recommends only temporary use. GOLD states that a few patients with viscous sputum may benefit, but that the overall benefits are low. According to NCCCC/NICE, mucolytic therapy should be considered in patients with a chronic cough productive of sputum and should be continued if there is a symptomatic improvement. For differences, see Areas of Differences.

Antitussives

GOLD and NCCCC/NICE both agree that antitussive therapy should not be used in the management of stable COPD. FMS does not offer recommendations.

Long-term Oxygen Therapy (LTOT)

All guidelines generally agree that LTOT should be considered in qualifying individuals, particularly individuals in advanced stages of COPD, in order to preserve vital organ function and extend life.

Smoking Cessation

All guidelines agree on the importance of promoting smoking cessation to prevent and/or slow down the progression of COPD.

Patient Education

GOLD and NCCCC/NICE agree that patient education is beneficial as part of a COPD management program to help patients cope with their illness as well as to meet specific objectives, such as education in smoking cessation. NCCCC/NICE cautions against using programs designed for asthma with COPD patients. FMS does not address patient education.

Surgery

All of the guidelines generally agree that surgery may be appropriate management of COPD in qualifying individuals. GOLD goes on to say that there is evidence that surgery (depending on the type of surgery) can reduce dyspnea and improve lung function, exercise capacity, global health, functional capacity, and quality of life.

Areas of Differences

Medical History

The guidelines vary on their approach to medical history taking. GOLD recommends taking a detailed and broad medical history. In contrast, NCCCC/NICE focuses on evaluating current signs and symptoms suggestive of COPD, particularly in patients over the age of 35, who are smokers or ex-smokers and have a chronic cough. FMS does not offer specific recommendations for medical history taking. The difference in approach is likely due to the broader scope of the GOLD guideline which includes a greater focus on risk assessment and prevention.

Physical Examination

Although there is general agreement among guidelines that physical examination is rarely diagnostic in COPD, GOLD emphasizes the importance of physical examination as a part of patient care and offers detailed recommendations (e.g., inspection, palpation and percussion, and ascultation). FMS also describes physical symptoms suggestive of severe COPD but notes that their absence does not exclude mild COPD. NCCCC/NICE offers no specific recommendations for physical examinations. They generally emphasize that diagnosis is suspected based on signs and symptoms that are supported by spirometry.

Assessing Severity of Disease

While all of the guidelines recommend a staging system based on FEV_1 values, the actual defining values and categories vary. For instance, the FMS guideline distinguishes between two different stages of disease (mild disease and continuous symptoms). NCCCC/NICE describes a three-stage system (mild, moderate, and severe). GOLD describes a five-stage system (at risk, mild, moderate, severe, and very severe).

GOLD points out that their staging system "should only be regarded as an educational tool, and a very general indication of the approach to management." It was not clinically validated. (See the classification scheme for each group Table below)

All three guidelines classify the severity of COPD based on airflow limitation as measured by spirometry. Different from the FMS and NCCCC/NICE guidelines, GOLD identifies an early stage of COPD (Stage 0), in which a person has chronic symptoms of COPD but normal spirometry. The Stage 0 category may be explained by the broader scope of the guideline with an additional focus on risk assessment and early preventive interventions.

Assessing Severity of COPD Disease

FMS (2005)
Mild disease: • Patients with occasional symptoms (generally FEV_1 >50% predicted) Continuous symptoms • Patients with continuous symptoms (generally FEV_1 <50% predicted)
GOLD (2005)
Stage 0 [At Risk]: • Normal spirometry • Chronic symptoms (cough, sputum production) Stage I [Mild COPD]: • FEV_1/FVC <70% • $FEV_1 \geq$80% predicted • With or without chronic symptoms (cough, sputum production) Stage II [Moderate COPD]: • FEV_1/FVC <70% • 50%$\leq FEV_1$ <80% predicted • With or without chronic symptoms (cough, sputum production) Stage III [Moderate COPD]: • FEV_1/FVC <70% • 30%$\leq FEV_1$ <50% predicted • With or without chronic symptoms (cough, sputum production) Stage IV [Very Severe COPD] • FEV_1/FVC <70% • FEV_1 <30% predicted or FEV_1 <50% predicted plus chronic respiratory failure
NCCCC/NICE (2004)

Mild airflow obstruction:

- 50 to 80% predicted FEV_1

Moderate airflow obstruction:

- 30 to 49% predicted FEV_1

Severe airflow obstruction:

- <30% predicted FEV_1

GOLD states that their categorization of severity is intended to be in-line with the recommendations that are being proposed by the COPD Guidelines Committee nominated jointly by the European Respiratory Society and by the American Thoracic Society (ATS/ERS). Instead of classifying severity of disease, NCCCC/NICE classifies severity of airflow obstruction, which they point out can be used to guide therapy and predict prognosis. The NCCCC/NICE guidelines are intended to harmonize with the values recommended by GOLD and the forthcoming ATS/ERS guidelines. Unlike FMS or GOLD, NCCCC/NICE recommends evaluation of BMI and exercise capacity in assessing severity, stating that results reflect the impact of the disease in an individual and predict prognosis.

Bronchodilator Reversibility Testing

There is some disagreement among guidelines on the indications for reversibility testing. GOLD points out that testing is generally performed at the time of diagnosis of moderate COPD and beyond, and is useful to help rule out a diagnosis of asthma, to establish a patient's best attainable lung function, and to gauge a patient's prognosis and to guide treatment decision. Likewise, FMS recommends testing with a bronchodilating drug at diagnosis and subsequent assessment of response, and as a component of the differential diagnosis for asthma. In contrast, NCCCC/NICE does not consider reversibility testing necessary or helpful for initial diagnostic process to plan initial therapy with bronchodilators or corticosteroids. They argue that results of testing may be unhelpful or misleading; asthma should be differentiated from COPD by features at the history and examination and longitudinal observations. Reversibility testing should be reserved to resolve diagnostic doubt.

Theophylline

There is some disagreement about the efficacy of methylxanthines. Citing a 2004 Cochrane review, FMS note that theophylline has a modest effect on FEV_1 and FVC and slightly improves arterial blood gas tensions in moderate to severe COPD. In contrast, GOLD states theophylline is effective in COPD (but not a preferred treatment due to toxicity). NCCCC/NICE reports that theophylline is effective in combination with $beta_2$-agonists or anticholinergics. In spite of possible efficacy, they all agree about proceeding with caution.

Corticosteroids

FMS recommend inhaled steroids only for patients with frequent exacerbations noting that they produce clinically very modest improvements compared to placebo in the long term. In contrast, GOLD and NCCCC/NICE recommend against a trial, citing evidence that shows that a trial of steroids is a poor predictor of response in COPD.

Mucolytic Therapy

While all guidelines generally agree that mucolytic therapy is appropriate at times, there is some disagreement. For instance, FMS states that any use should be temporary. On the other hand, NCCCC/NICE recommends ongoing mucolytic therapy in patients with a chronic cough productive of sputum who have received symptomatic improvement from the mucolytic therapy. NCCCC/NICE bases the recommendations on evidence of benefit.

Antioxidant Agent

Although FMS does not comment on the role of antioxidants, GOLD and NCCCC/NICE differ in perspectives. NCCCC/NICE recommends against antioxidant supplements (alpha-tocopherol and beta-carotene), alone or in combination. GOLD states that antioxidants, in particular N-acetylcysteine, have been shown to reduce the frequency of exacerbations and could have a role in the treatment of patients with recurrent exacerbations. They withhold recommendations for routine use pending careful evaluation of ongoing trials.

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